ALKALOIDS OF Veratrum, Petilium, AND Korolkowia

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The review is devoted to a study of the steroid alkaloids of plants of the genera Veratrum, Petilium, and Korolkowia. Characteristic reactions, spectra, and some chemical transformations of the alkaloids subdivided into groups according to structure are discussed. Some methods for determining their structures are considered.

The genera Veratrum (false hellebore), Petilium, and Korolkowia belong to the family Liliaceae. In the flora of the world, 25 species of the genus Veratrum have been described, and in the USSR seven, including two in Central Asia (V. lobelianum and V. nigrum) [1-3]. The alkaloids of 11 species of Veratrum have been investigated: from V. lobelianum Bernh. 47 have been isolated; from V. album L., 39; from V. viride Air., 17; from V. grandiflorum O. Loes, 10; from V. eschscholtzii A. Gray, 8; from V. oxysepalum Turcz, 6; from V. fimbriatum A. Gray, 6; from V. nigrum L., 3; from V. californicum, 3; from V. stamineum Maxim, 3; and from V. schindleri O. Loes, 2 alkaloids.

The alkaloids pseudojervine and neogermitrine are found in five species, germerine in four, neogermbudine, protoveratridine, protoveratrine A, germbudine, solanidine, protoveratrine B, veratrosine, germitetrine, 11-deoxojervine, germanitrine, isorubijervine, germine, veralkamine, veralinine, angeloylzygadenylic acid lactone, zygadenylic acid lactone, and veramine in two, veramarine, zygacine, and rubijervine in four, veratramine and veratroylzygadenine in six, and jervine in almost all the species of Veratrum that have been studied.

Thus, from 11 species of Veratrum growing on the terrestrial globe, 87 alkaloids have been isolated; 25 of them are bases of undetermined structure, and these are not considered in the present paper.

In the USSR, from various parts of the plant V. lobelianum growing in the North Caucasus 12 known bases have been isolated (jervine, germidine, protoveratrine A, rubijervine, isorubijervine, germitetrine, veramarine, veralkamine, veralinine, verazine, veramine, and germerine) and three new alkaloids (deacetylprotoveratrine A, dideacetylprotoveratrine A, and loveraine [4-12]). From the roots of V. lobelianum and V. nigrum collected in various regions of the Tomsk province have been isolated jervine, rubijervine, and verazine [13, 14]. Jervine and pseudojervine have been found in the roots and rhizomes of V. lobelianum growing in the Stepanavan region of the Armenian SSR [15], and seven uncharacterized bases in the hypogeal parts of the plant growing in the region of Lake Issyk-Kul', Kirghiz SSR [16, 17].

We are the first to have investigated the epigeal and hypogeal parts of V. lobelianum growing in the Karkara valley, and also the epigeal part of this plant collected at Dzhergalan, Kirghiz SSR, and have isolated 24 alkaloids, 10 of them being new; deacetylveralosine and veralomidine have been isolated from this plant for the first time, and γ-solanine from the genus Veratrum for the first time [18-29].

Of the seven species of Veratrum growing on the territory of the USSR it is mainly one species (V. lobelianum) that has been subjected to chemical investigation, and 43 alkaloids have been isolated from it.

The genus Petilium is represented by two species: Petilium eduardi (Rgl.) Vved. and Petilium raddeana (Rgl.) Vved. Both are perennial bulbaceous plants growing in the mountain regions of Central Asia and outside the USSR in Afghanistan [30]. From plants of P. eduardi collected in Shargun' and Babatag, Surkhandar'ya province, have been isolated imperialine (sipaimaine, raddeanine) [31-38], edpetilidine, eduardine [37], edpetiline, peimisine [39], imperialone, imperialine N-oxide, edpetilidinine, edpetilinine, edpetine, eduardinine, edpetisine, edpetisinine, and edpetisidine [40-51]. Imperialine N-oxide is the first representative of N-oxides among the steriod alkaloids.

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P. raddeana is widely distributed in the Turkmen SSR and in the foothills of the Kopet Dagh. From the bulbs of this plant have been isolated imperialine (raddeanine), raddeamine, alvanine, alvanidine, and two uncharacterized bases [32, 33], and from the epigeal part of P. raddeana collected in the Kizilarvat region of Ashkhabad province imperialine, edpetiline, petiline, petilinine, petilidine, and petilidinine [31, 52, 53].

A total of 23 alkaloids has been isolated from plants of the genus Petilium.

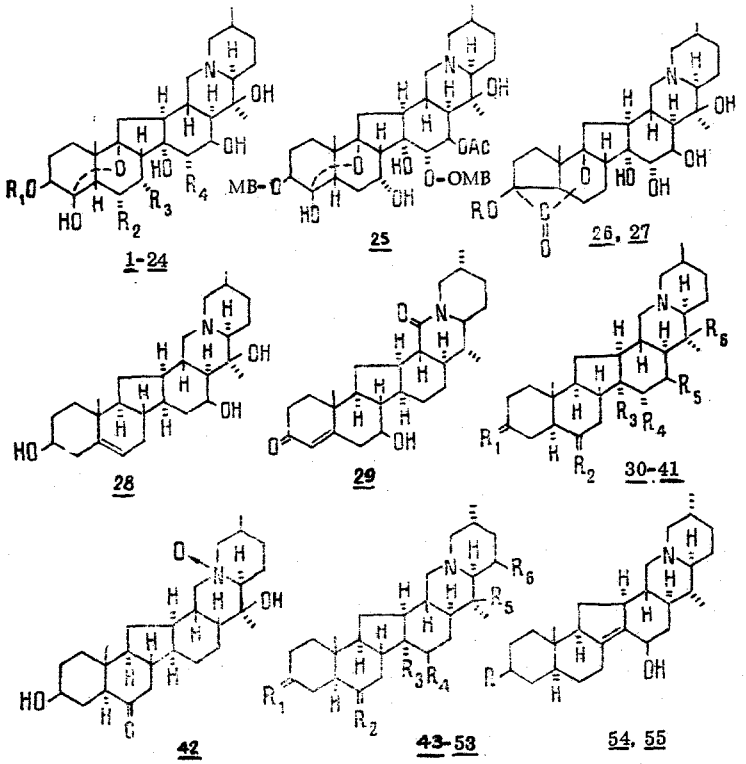
The genus Korolkowia is represented by one species – Korolkowia sewerzowii. This perennial bulbaceous plant grows in the foothills on clayey and rocky slopes. It is widely distributed in Central Asia (the Tien-Shan, the Pamir-Alai, the Pamir-Alai, the Chatkal valley, and at Khamzaabad and Saryagach pod Tashkentom) [54-61]. From the bulbs and epigeal part of the plant collected at various growth sites (Chatkal valley, Khamzaabad, Saryagach pod Tashkentom, and Katrantau, KirgSSR) a number of alkaloids has been isolated: alginine, algamine [62, 63], korsevine, korsine, korseveriline, korsinine, sevcorine, korseverine, algininide, korseverinine, korseveridine, korseveramine, korsevinine [55-61], severtzidine, korseveridinine, korsidine, korsiline, severine, sevedine, and korsinamine [64-70]. A total of 20 alkaloids has been isolated from K. sewerzowii.

The alkaloids of Veratrum, Petilium, and Korolkowia belong to the typical steroid and C-nor-D-homosteroid alkaloids and are derivatives of 3-methyl-1,2-cyclopentenophenanthrene and of 1,2-benzofluorene with a nitrogen-containing heterocyclic system. In accordance with the structures of the main heterocyclic skeleton they are divided into groups: the cevine and jervine groups and the veratramine, solanidine, and verazine groups. In addition, new steroid alkaloids of the types of veralkamine, edpetilidinine, and veracintine [71-73] have been detected.

Below we give a list of the alkaloids of the plants of the genera under consideration:

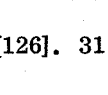
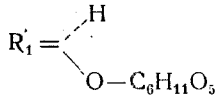
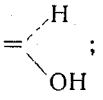
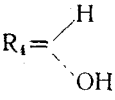
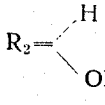
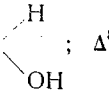
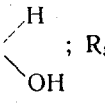
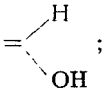
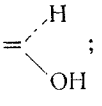
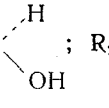
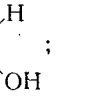
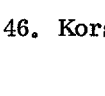
I. C-NOR-D-HOMOSTEROID ALKALOIDS

1. Cevine Group*



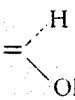
1. Germine. $R_1 = R_2 = H$; $R_3 = R_4 = OH$; V. viride [82, 110]. 2. Germidine. $R_1 = Ac$; $R_2 = H$; $R_3 = OH$; $R_4 = O$-MB. V. viride [10, 111, 112]. 3. Neogermidine. $R_1 = R_2 = H$; $R_3 = OAc$; $R_4 = O$-Mb. V. viride [112].

*Abbreviations of the acids present in ester alkaloids: Ac) acetic; MB) 2-methylbutyric; HMB) 2-hydroxy-2-methylbutyric; DMB) 2,3-dihydroxy-2-methylbutyric; An) angelic; Ve) veratric; and Va) vanillic.

4. Neogermitrine. R_1 = Ac; R_2 = H; R_3 = OAc; R_4 = O-MB. V. lobelianum, V. album, V. eschscholtzii, V. fibriatum, V. viride [26, 110, 112]. 5. Germerine. R_1 = MB; R_2 = H; R_3 = OH; R_4 = O-OMB. V. album, V. nigrum, V. lobelianum, V. viride [12, 21, 110, 112, 113]. 6. Germbudine. R_1 = (+)-threo-DMB; R_2 = H; R_3 = OH; R_4 = O-MB. V. lobelianum, V. viride [29, 92, 114]. 7. Neogermbudine. R_1 = (−)-erythro-DMB; R_2 = H; R_3 = OH; R_4 = O-MB. V. album, V. viride [92, 110, 112]. 8. Germanitrine. R_1 = An; R_2 = H; R_3 = OAc; R_4 = O-MB. V. fimbriatum, V. lobelianum [26, 110, 112, 115]. 9. Germitrine. R_1 = MB; R_2 = H; R_3 = OAc; R_4 = O-HMB. V. viride [111, 112]. 10. Germitetrine. R_1 = CO-C(OH)(CH_3)-CH(OAc)-CH_3; R_2 = H; R_3 = OH; R_4 = O-MB. V. album [12, 112, 116]. 11. Protoveratridine. R_1 = MB; R_2 = R_3 = R_4 = H. V. album, V. viride [110, 112]. 12. 15-Veratroylgermine. R_1 = R_2 = H; R_3 = OH; R_4 = O-Ve. V. album [117]. 13. 3-Acetyl-15-veratroylgermine. R_1 = Ac; R_2 = H; R_3 = OH; R_4 = O-Ve. V. album [117]. 14. Deacetylprotoveratrine A. R_1 = HMB; R_2 = OAc; R_3 = OH; R_4 = O-MB. V. lobelianum [11, 110, 117]. 15. Dideacetylprotoveratrine A. R_1 = HMB; R_2 = R_3 = OH; R_4 = O-MB. V. lobelianum [12, 118]. 16. Deacetylprotoveratrine B. R_1 = DMB; R_2 = OAc; R_3 = OH; R_4 = O-HMB. V. album [119, 120]. 17. Protoveratrine A. R_1 = HMB; R_2 = R_3 = OAc; R_4 = O-HMB. V. viride, V. lobelianum, V. album [8, 82, 110, 118]. 18. Protoveratrine B. R_1 = (+)-threo-DMB; R_2 = R_3 = OAc; R_4 = O-MB. V. viride, V. album [82, 110]. 19. Escholerine. R_1 = An; R_2 = R_3 = OAc; R_4 = O-MB. V. eschscholtzii [114]. 20. Angeloylzygadenine. R_1 = An; R_2 = R_3 = H; R_4 = OH. V. stamineum [84, 121]. 21. Veratroylzygadenine. R_1 = Ve; R_2 = R_3 = H; R_4 = OH. V. album, V. oxysepalum, V. lobelianum, V. eschscholtzii, V. fimbriatum, V. nigrum [21, 84, 110, 122]. 22. Zygacine. R_1 = Ac; R_2 = R_3 = H; R_4 = OH. V. album, V. grandiflorum, V. oxysepalum [84, 110, 122]. 23. Germinalinine. R_1 = DMB; R_2 = H; R_3 = OAc; R_4 = O-HMB. V. lobelianum [29]. 24. Zygadenine. R_1 = R_2 = R_3 = H; R_4 = OH. V. album [84, 121]. 25. Germinaline. V. lobelianum [20]. 26. Zygadenylic acid lactone. R = H. V. oxysepalum, V. album [121, 123]. 27. Angeloylzygadenylic acid lactone. R = An. V. album, V. grandiflorum [124]. 28. Veramarine. V. album, V. viride, V. lobelianum [12, 125, 148]. 29. Veralodine. V. lobelianum [22]. 30. Veratrenone. R_1 = O; Δ^4; R_2 = 2H; R_4 = H; R_3 = R_5 = R_6 = OH. V. lobelianum [126]. 31. Imperialine. R_1 =  ; R_2 = O; R_3 = R_4 = R_5 = H; R_6 = OH. P. eduardi, P. raddeana [31-38, 95]. 32. Imperialone. R_1 = R_2 = O; R_3 = R_4 = R_5 = H; R_6 = OH. P. eduardi [36, 37, 40]. 33. Edpetiline. R_1 =  ; R_2 = O; R_3 = R_4 = R_5 = H; R_6 = OH. P. eduardi [40]. 34. Edpetilidine. R_1=R_2=  ; R_3 = R_4 = R_5 = R_6 = H. P. eduardi [40, 96]. 35. Eduardine. R_1 =  ; R_2 = O; R_3 = R_4 = R_5 = R_6 = H. P. eduardi [40, 96]. 36. Eduardinine. R_1 =  ; R_2 =  ; R_3 = R_4 = R_5 = R_6 = H. P. eduardi [47]. 37. Edpetisine. R_1 = O; R_2 = 2H; Δ^8; R_3 = R_4 = R_5 = H; R_6 = OH. P. eduardi [48]. 38. Edpetisinine. R_1=R_4=  ; R_2=  ; R_3=R_5=R_6=H. P. eduardi [50]. 39. Korseverine. R_1=  ; R_2=O; $\Delta^{8(9)}$; R_3=R_4=R_5=R_6= H. K. sewerzowii [55, 57, 58]. 40. Korsinine. R_1=R_2=  ; $\Delta^{8(9)}$; R_3=R_4=R_5=R_6=H. K. sewerzowii [58]. 41. Severtzidine. R_1 =R_2=  ; R_3=OH; R_4=R_5=R_6=H. K. sewerzowii [64]. 42. Imperialine N-oxide. P. eduardi [49]. 43. Edpetisidine. R_1=  ; R_2=  ; $\Delta^{8(9)}$; R_3=R_4=R_6=H; R_5=OH. P. eduardi [51]. 44. Petilidine R_1=  ; R_2=  ; R_3=R_4=R_5=R_6=H. P. raddeana [52]. 45. Petilinine. R_1=R_2=  ; R_3=R_4=R_5=R_6= H. P. raddeana [52]. 46. Korseverinine. R_1=R_2=  ; $\Delta^{8(9)}$; R_3=R_4=R_5=R_6=H. K. sewerzowii

[60]. 47. Korsidine. $R_1=$  ; $R_2=$  ; $\Delta^{8(9)}$; $R_3=R_4=R_5=R_6=H$. K. sewerzowii [65]. 48. Korsine.

$R_1=R_2=$  ; $\Delta^{8(9)}$; $R_3=R_4=R_5=H$; $R_6=OH$. K. sewerzowii [57, 58]. 49. Korsinamine. $R_1=R_2=$  ; $\Delta^{8(9)}$;

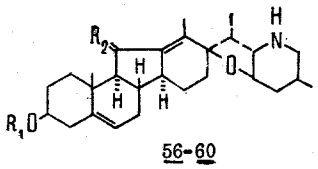
$R_3=R_4=R_5=H$; $R_6=OAc$. K. sewerzowii [70]. 50. Korseveriline. $R_1=$  ; $R_2=$  ; $R_3=OH$; $R_4=R_5=R_6=H$.

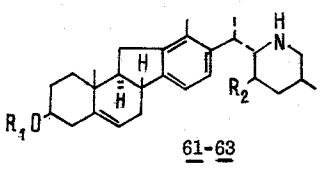
K. sewerzowii. 51. Korseveramine. $R_1=R_2=$  ; $R_3=OH$; $R_4=R_5=R_6=H$. K. sewerzowii. 52. Sevedine.

$R_1=R_2=$  ; $R_3=OH$; $R_4=R_5=R_6=H$. K. sewerzowii [69]. 53. Severine. $R_1=$  ; $R_2=$  ; $R_3=OH$;

$R_4=R_5=R_6=H$. K. sewerzowii [68]. 54. Korseveridine. R = —OH. K. sewerzowii [55, 57]. 55. Korseveridinine. R = ···OH. K. sewerzowii [66].

2. Jervine and Veratramine Group


56-60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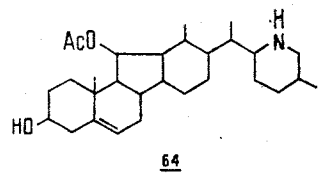
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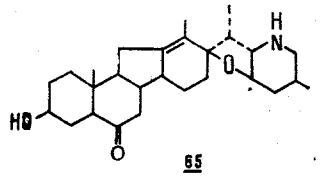
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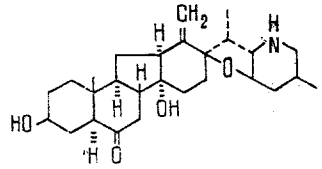
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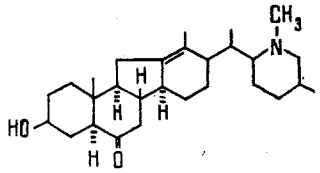
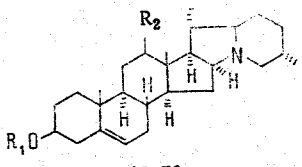

67

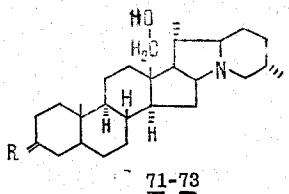
56. Jervine. $R_1 = H$; $R_2 = O$. V. album, V. grandiflorum, V. lobelianum, V. oxysepalum, V. eschscholtzii, V. fimbriatum, V. nigrum, V. stamineum, V. viride [6, 8, 13-15, 21, 98, 110]. 57. Pseudojervine. $R_1 = C_6H_{11}O_5$; $R_2 = O$. V. album, V. lobelianum, V. eschscholtzii, V. fimbriatum, V. viride [15, 21, 98, 110]. 58. Veratrobasine. $R_1=H$; $R_2=$  . V. album [127, 128]. 59. 11-Deoxojervine (cyclopamine). $R_1 = H$; $R_2 = 2H$. V. album, V. grandiflorum [77]. 60. Cycloposine. $R_1 = C_6H_{11}O_5$, $R_2 = 2H$. V. californicum [129]. 61. Veratramine. $R_1 = H$; $R_2 = OH$. V. album, V. grandiflorum, V. oxysepalum [98, 110, 130, 131]. 62. Veratrosine. $R_1 = C_6H_{11}O_5$; $R_2 = OH$. V. eschscholtzii, V. viride [110, 131, 132]. 63. Verarine. $R_1 = R_2 = H$. V. album [133, 134]. 64. Muldamine. V. californicum [135]. 65. Peimisine. P. eduardi [40, 42, 99]. 66. Edpetine. P. eduardi [46]. 67. Korsevine. K. sewerzowii [55, 56].

II. TYPICAL STEROID ALKALOIDS

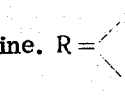
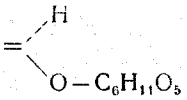
1. Solanidine Group



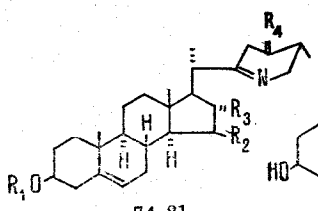
68-70



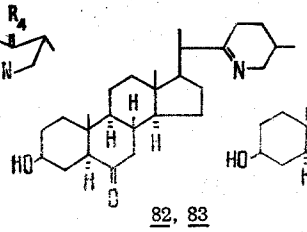
71-73

68. Solanidine. $R_1 = R_2 = H$. V. californicum, V. lobelianum [26, 77, 136, 137]. 69. γ-Solanine. R_1 = galactose; $R_2 = H$. V. lobelianum [26, 138]. 70. Rubijervine. $R_1 = H$; $R_2 = OH$. V. album, V. grandiflorum, V. lobelianum, V. oxysepalum, V. eschscholtzii, V. nigrum, V. viride [11, 13, 14, 139-141]. 71. Isorubijervine. R =  ; Δ^5. V. album, V. lobelianum, V. eschscholtzii, V. viride [11, 141, 142]. 72. Isorubijervosine. R =  ; Δ_5. V. eschscholtzii [132]. 73. Veralobine. R = O; Δ^4. V. album [14].

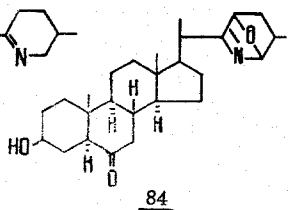
2. Verazine Group



74-81



82, 83



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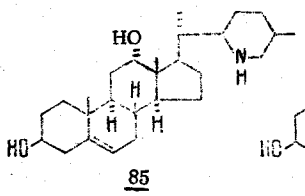

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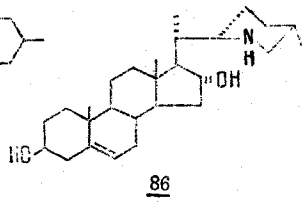

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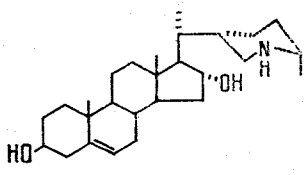

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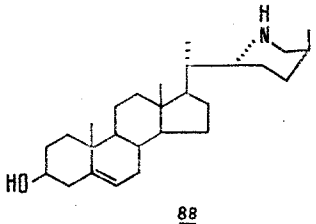
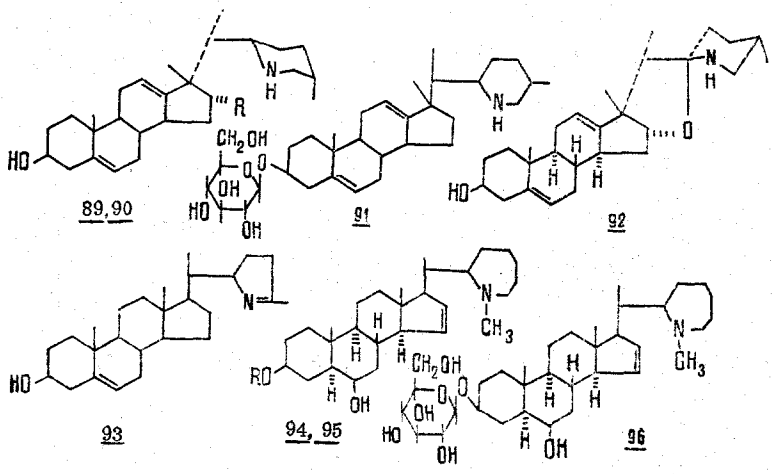


88

74. Verazine. $R_1 = R_2 = R_3 = H$; $R_4 = 2H$. V. lobelianum [12-14, 72, 140]. 75. Veralosidine, etioline. $R_1 = R_2 = H$; $R_3 = OH$; $R_4 = 2H$. V. lobelianum, V. grandiflorum [18, 19, 101]. 76. Veralosinine. $R_1 = R_2 = H$; $R_3 = OAc$; $R_4 = 2H$. V. lobelianum [19]. 77. Veralosine. $R_1 = C_6H_{11}O_5$; $R_2 = H$; $R_3 = OAc$; $R_4 = 2H$. V. lobelianum [18]. 78. Deacetylveralosine. $R_1 = C_6H_{11}O_5$; $R_2 = H$; $R_3 = OH$; $R_4 = 2H$. V. lobelianum [18, 27]. 79. Veralodisine. $R_1 = R_2 = H$; $R_3 = OAc$; $R_4 = O$. V. lobelianum [24]. 80. Veralodinine. $R_1 = C_6H_{11}O_5$; $R_2 = H$; $R_3 = OAc$; $R_4 = O$. V. lobelianum [25]. 81. Veralosidinine. $R_1 = H$; $R_2 = OH$; $R_3 = OAc$; $R_4 = 2H$. V. lobelianum [23]. 82. Petiline.* P. raddeana [52]. 83. Korsiline.* K. sewerzowii [67]. 84. Korsevenine. K. sewerzowii [59]. 85.

* Petiline and korsiline are stereoisomers at C_{21} or (and) C_{23} – Translator.

3. New Types of Steroid Alkaloids



Baikeine. V. grandiflorum [102]. 86. Teinemine. V. grandiflorum [144]. 87. Isoteinemine. V. grandiflorum [144]. 88. Veramiline. V. lobelianum [145].

89. Veralkamine. R = OH. V. album, V. lobelianum [12, 61, 146]. 90. Veralinine. R = H. V. album, V. lobelianum [12, 107]. 91. Veralomine. V. lobelianum [28]. 92. Veramine. V. album [106]. 93. Veracintine, V. album [73]. 94. Edpetilidinine. R =H. P. eduardi [40, 105]. 95. Edpetilinine. R = xylose. P. eduardi [45]. 96. Sevkorine. K. sewerzowii [57, 61].

In the determination of the basic heterocyclic skeleton and the establishment of the structure and stereochemistry of the steroid alkaloids, in combination with chemical methods wide use is being made of physical methods of investigation (UV, IR, NMR, and mass spectrometry, ORD, CD, etc.).

The presence in the UV spectra of steroid alkaloids of maxima at 280-300 nm (log ε 1.7-2.07) and 236-255 nm (log ε 4.2-4.26), and at 300-340 nm (log ε 1.89-2.75) shows the presence of isolated carbonyl groups and of α,β-unsaturated ketones, respectively [36, 41, 58, 74]. Maxima at 268 nm (log ε 2.8) are characteristic for a substituted benzene ring [75], and a maximum at 240-243 nm shows the presence of a C = N chromophore in the alkaloid [72].

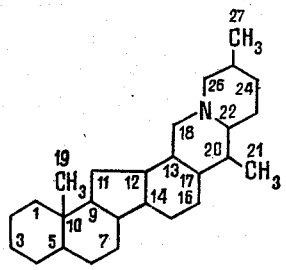
In the IR spectra of the alkaloids, absorption bands are observed at 3640-3140 and 1080-1020 cm^{-1} (hydroxy and secondary amino groups), 2980-2820 and 1470-1430 cm^{-1} methylene and methyl groups), 1780-1690 cm^{-1} (carbonyl group), 1745-1723, 1270-1230, 1140-1025 cm^{-1} (ester carbonyl), 2790-2770 cm^{-1} (N-methyl group), 1650-1680 cm^{-1} (C = N double bond), and 2790-2740 cm^{-1} (trans-quinolizidine) [41, 55-60, 76, 91]. An absorption band at about 1050 cm^{-1} shows the presence of a 3β-one-Δ^5 system [77].

In the NMR spectra, chemical shifts (CSs) at 4.50-4.70 ppm show the presence of axially oriented protons geminal to acetoxy groups, and shifts at 4.73-5.05 ppm show equatorially oriented protons [38, 50, 51, 66, 70]. In the mass spectra, strong peaks of ions with m/e 110, 111, 112, 114, and 220 [37, 52, 57, 78] are characteristic for C-nor-D-homosteroid alkaloids, and peaks of ions with m/e 82, 98, 114, 125, and 150 formed by the same scheme [37, 42, 52, 57] are characteristic for the typical steroid alkaloids.

I. C-NOR-D-HOMOSTEROID ALKALOIDS

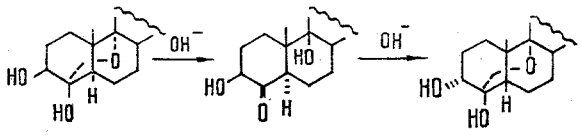
1. Cevine Group

Alkaloids of the cevine group are found in the form of free amino alcohols and as ester alkaloids and glucoalkaloids. From the genus Veratrum have been isolated 30 alkaloids of the cevine group, from Petilium 12, and from Korolkowia 13. Cevine alkaloids are also found in plants of the genera Zygadenus, Schoenocaulon, and Fritillaria. The alkaloids of this group are based on a heterocyclic skeleton which has been called cevanine (I) [79].



I

Some alkaloids of the cevanine series contain an α-ketol system (cevine [80], veracevine [81], germine [82], protoverine [83], zygadenine [84], and the ester alkaloids derived from them). The presence of an α-ketol system is confirmed by their conversion in weakly alkaline solution into carboxyl-containing compounds which, in concentrated caustic potash solution, readily isomerize to form iso compounds [85-87]:



The nature and positions of the hydroxy groups of the alkaloids have been established by a study of the corresponding products obtained on acetylation and on oxidation with chromic acid and sodium periodate, and also by the production of acetonides [80, 82, 83, 85].

The NMR spectra of the alkaloids contain the signals from the protons of two tertiary and one secondary or two secondary and one tertiary C-methyl groups [88]. The chemical shifts of the C-19, C-21, and C-27 methyl protons change according to the nature, positions, and configurations of the substituents in rings A, B, C, D, E, and F. The A/B, B/C, and C/D ring linkages are determined from the CSs of the protons of the C-19 methyl groups. In the case of a trans A/B ring linkage the protons of the C-19 methyl group resonate at 0.68-0.97 ppm and in the case of cis linkage at 0.97-1.04 ppm [38, 57, 59, 60, 89, 90]. In the quinolizidine moiety of the molecule the signals of equatorially oriented methyl protons appear at 0.68-0.85 ppm and of axially oriented methyl protons at 1.00-1.04 ppm [38, 88, 89]. When a tertiary hydroxy group is present at C_{20}, the chemical shift of the C-21 methyl group is observed at 0.68-1.45 ppm in the form of a singlet [37, 38, 52, 88, 89]. The formation of peaks of ions with m/e 154, 155, 156 in the mass spectra of the cevine alkaloids also shows the presence of a tertiary hydroxy group at C_{20} [37].

Saponification of the ester alkaloids leads to the splitting out of acetic, *l*-2-hydroxy-2-methylbutyric, d-2-methylbutyric, *l*-2,3-dihydroxy-2-methylbutyric, d-2,3-dihydroxy-2-methylbutyric, angelic, tiglic, veratric, or vanillic acid. The positions of the acyl radicals in the ester alkaloids are established mainly by hydrolysis under various conditions, by methanolysis, and by oxidation with periodic and chromic acids. The amino alcohols of the majority of Veratrum ester alkaloids are germine [82], protoverine [83], and zygadenine [84].

The saponification of germinaline and germinalinine gives the amino alcohol germine. The structure of germinaline is confirmed by its conversion into acetylgermine [20], and that of germinalinine by its conversion into triacetylgermbudine [29, 92].

The heterocyclic skeleton of veralodine and of the other alkaloids considered below has been established from the results of NMR and mass spectroscopy of the bases and the products of their transformations or by passage to known compounds.

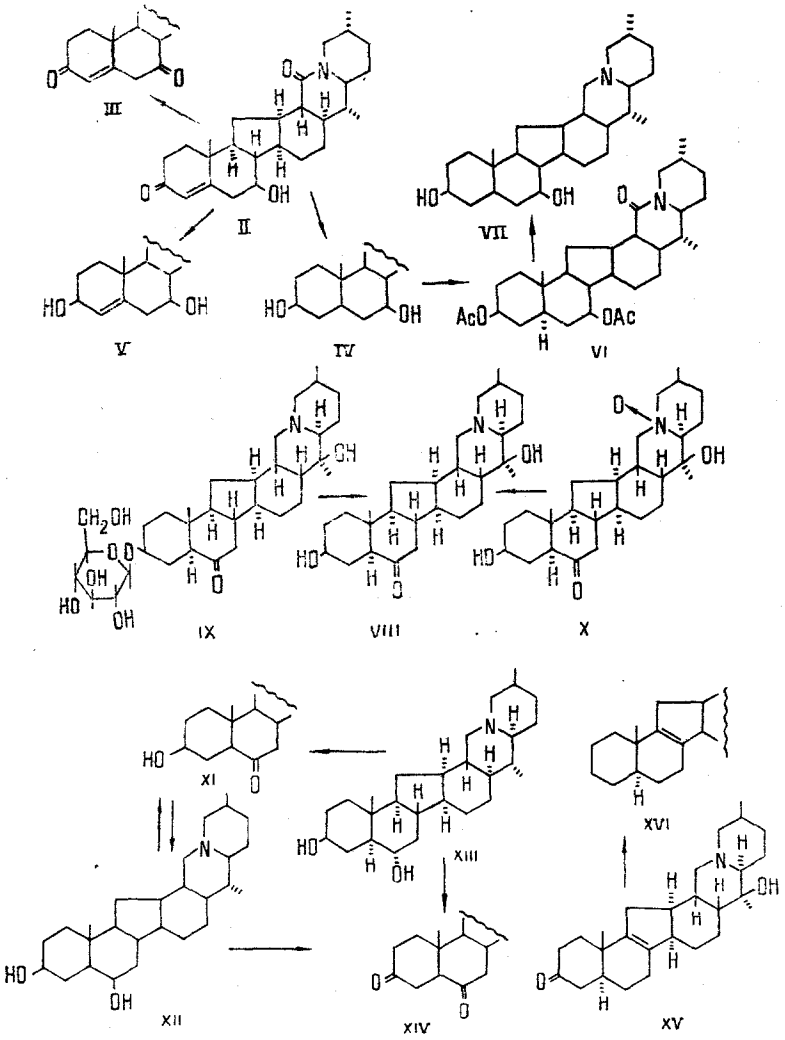
Veralodine contains an α,β-unsaturated ketone grouping, a lactam carbonyl, and hydroxy groups [22]. The oxidation of veralodine (II) with chromium trioxide in acetic acid forms the diketone veralodinone (III). The Adams hydrogenation of veralodine gives tetrahydroveralodine (IV), and its reduction with lithium tetrahydroaluminate gives dihydroveralodine (V). On reduction with lithium tetrahydroaluminate, diacetyltetrahydroveralodine (VI) gives deoxotetrahydroveralodine (VII), the IR spectrum of which contains absorption bands at 3285 cm^{-1} (OH) and 2787 cm^{-1} (trans-quinolizidine) [91].

As a result of a study of the chemical shift of the protons of the 19-CH_3, 21-CH_3, and 27-CH_3 methyl groups in the NMR spectra of veralodine and its dihydro, acetyl, oxidized, and deoxytetrahydro derivatives it has been established that the carbonyl group is present in position 3 and the double bond between carbon atoms 4 and 5 [22, 93], while the lactam carbonyl is at C-18 and the hydroxy group at C-7. The presence of an α,β-

unsaturated carbonyl group in ring A is also confirmed by the circular dichroism curves in the spectrum of veralodine. The circular dichroism spectrum of veralodine [94] has three Cotton effects. Two of them, at 315 nm ($\Delta\varepsilon$ −1.54) and at 240 nm ($\Delta\varepsilon$ +8.8), respectively, are due to n → π^* π → π^* transitions in the α,β-unsaturated carbonyl chromophore.

The structure and configuration of imperialine (VIII) have been confirmed by an x-ray structural analysis of imperialine hydrobromide, which showed the cis-linkage of rings D/E [95]. The glycoalkaloid edpetiline (IX) has the structure of 3β-O-D-glucopyranosylimperialine. The natural N-oxide of imperialine (X) proved not to be identical with the synthetic N-oxide obtained by the oxidation of imperialine with hydrogen peroxide. It has been established that the imperialine N-oxide found in nature and that produced by synthesis are isomeric N-oxides [49].

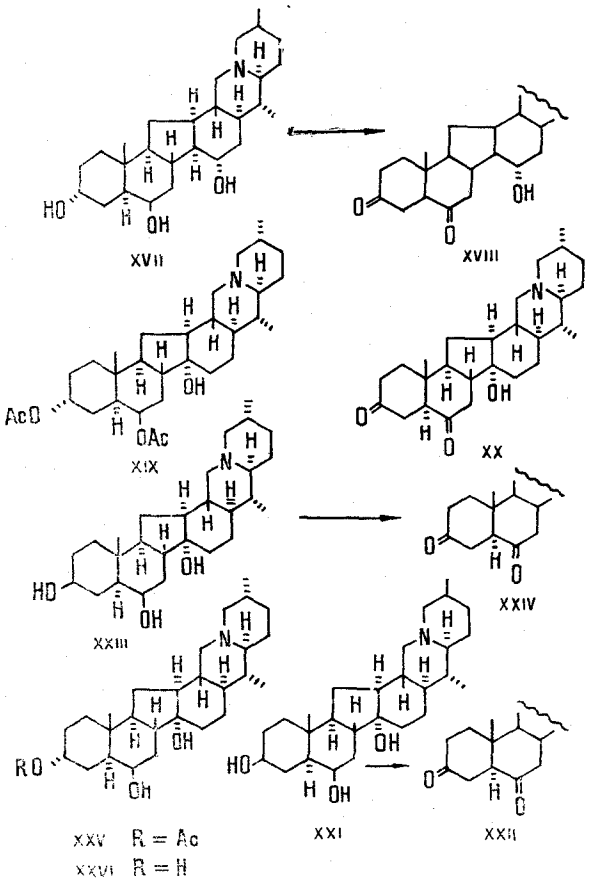
The reduction of eduardine (XI) gives edpetilidine (XII), and the oxidation of edpetilidine with chromium trioxide in acetic acid gives eduardine. The oxidation of eduardinine (XIII) also gave eduardine (XI) and a diketone (XIV) identical with the diketone obtained by the oxidation of edpetilidine. The presence of a 3β-oriented hydroxy group at C_3 and a carbonyl group at C_6 in eduardine and korseverine has been established by comparing the difference of the CSs of the 19-CH_3 protons in the NMR spectra of these bases and their acetyl derivatives with those for imperialine and acetylimperialine [47, 57].



The Huang-Minlon reduction of edpetisine (XV) gives deoxodihydroedpetisine (XVI). The position of the double bond in edpetisine at C_8-C_9 and of the carbonyl group at C_3 is shown by a determination of the downfield shift of the signals of the protons of the 19-CH_3 group in the NMR spectra of edpetisine and deoxodihydroedpetisine as compared with those for deoxodihydroimperialone and deoxytetrahydroimperialone [36, 48]. The double bond at C_8-C_9 in korseverine, korseverinine, korsinine, and edpetisidine is also shown by a determination of the downfield shift of the signals of the protons of the 19-CH_3 group in their NMR spectra as compared with those

for the dihydro derivatives [57, 58, 60].

A comparison of the CSs of the protons of the 19-CH_3 groups in the NMR spectra of edpetisinine (XVII) [50] and of the diketone of edpetisinine (XVIII) with those of diacetylkorseveriline (XIX) and korseverilinedione (XX) shows that the two hydroxyls in edpetisinine are located at C_3 and C_6. The changes in the CSs of the protons of the 19-CH_3 group in the NMR spectra of edpetilidine [96], eduardinine [47], edpetisidine [51], petilidine [52], korsinine [58], korseverinine [60], korsidine, korsine, korsinamine, korseveriline, korseveramine, sevedine, and severtzidine and the acetyl and oxidized derivatives show that these alkaloids also contain hydroxy groups at C_3 and C_6 [57, 64, 65, 69, 70]. Petilinine and petilidine are isomeric compounds with respect to the hydroxy group at C_3 [52]. Korsinine is an alkaloid closely related to korseverine. The oxidation of korsinine forms a ketone – korsininone – which is identical with korseverinone [57, 58].



The position of the hydroxy group at C_{15} in each of the alkaloids korseveridine, korseveridinine, and edpetisinine is shown by the presence in the mass spectra of the peaks of ions with m/e 111, 112, 149, 164, and 179 [50, 57, 66].

On acetylation, korseveridine [57] forms diacetylkorseveridine, and on Oppenauer oxidation it forms korseveridinone. The position of the double bond in korseveridine at C_8–C_{14} has been established by a determination of the appearance of the signal from the protons of the 19-CH_3 group in the NMR spectra of diacetylkorseveridine and korseveridinone in a stronger field than in the case of similar dihydro derivatives of model compounds [57].

The structure of korseveridinine is confirmed by its conversion into korseveridinone [57], and that of korsidine by its conversion into petilininedione [52]. In korsine, the hydroxy group at C_{23} is shown by the presence in the mass spectra of korsine and its products of strong peaks of ions with m/e 127, 128 in place of the ions with m/e 111 and 112 that are formed from ring F. The structure 23β-acetylkorsine has been established for korsinamine [57, 58].

The oxidation of severtzidine (XXI) forms a diketone – severtzidinedione (XXII) – and its acetylation form diacetylsevertzidine. Severtzidine is similar in structure to the alkaloids korseveriline and sevedine. However, severtzidinedione is not identical with korseverilinedione and sevedinedione [64, 69]. In the mass spectra of

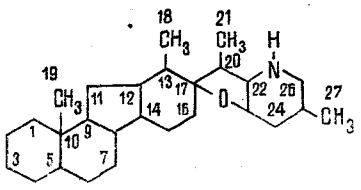
korseveriline, korseveramine, and severtzidine the peaks of ions with m/e 162, 164, and 178 show the presence of a hydroxy group at C_{14}. The hydroxyl at C_{14} can also be shown by the results of NMR spectroscopy, i.e., when an OH group is present at C_{14}, there are no changes in the chemical shifts of the protons of the secondary and tertiary methyl groups [57, 58, 60, 64].

The oxidation of sevedine (XXIII) forms a diketone sevedinedione, identical with korseverilinedione (XXIV). This confirms the structure of sevedine [69]. Severine (XXV) is a monoacetyl derivative of korseveriline (XXVI) and has the structure of 3α-acetylkorseveriline [68].

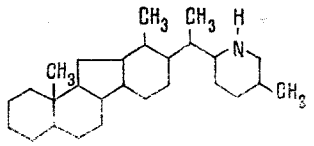
Korseveriline [57, 58], korseveramine [60], and sevedine [69] are isomeric compounds with respect to the hydroxy groups at C_3 and C_6.

2. Jervine and Veratramine Group

The alkaloids of the jervine and veratramine group are found in various species of the genus Veratrum and in the plants P. eduardi and K. sewerzowii. The jervine group includes six alkaloids from the genus Veratrum, two from Petilium, and one from Korolkowia, and the veratramine group includes three alkaloids only from the genus Veratrum. The alkaloids jervine and veratramine contain the heterocyclic skeleton of jervanine (XXVII) and veratranine (XXVIII).



XXVII



XXVIII

The alkaloids of these groups, apart from korsevine, are secondary bases and are found in nature in the form of free amino alcohols, glycoalkaloids, and rarely, ester alkaloids. They contain four C-methyl groups and double bonds; the oxygen atoms in the molecule are found in the form of carbonyl and hydroxy groups. In the majority of the alkaloids of the jervine group one of the oxygen atoms forms an ether bridge between carbon atoms C_{17} and C_{23} which is split under the action of acids, forming iso compounds [74, 97]. Oxidation of the alkaloids of the veratramine group with potassium permanganate gives benzene-1,2,3,4-tetracarboxylic acid [75].

The NMR spectra of the alkaloids of the jervine and veratramine group each contain the signals from four C-methyl groups. The chemical shifts of the C-19, C-18, C-21, and C-27 methyl protons change according to the nature, position, and configuration of the substituents in the rings. It is possible to determine the A/B and B/C ring linkages from the CSs of the protons of the C-19 methyl group [52, 93]. The protons of the C-18 methyl group resonate at 1.6-2.3 ppm.

In the alkaloids of the jervine group, the signals of the protons of the C-19 methyl group appear in the form of sharp singlets at 0.71-1.42 ppm. Substituents on the nitrogen atom, and also a Δ^{12}-double bond, do not affect the CSs of the protons of the C-19 methyl group, which resonate at 0.71-1.23 ppm; the protons of the C-21 and C-27 methyl groups appear in the form of separate doublets at 0.82-1.06 ppm [42, 46, 90].

Peimisine – an alkaloid structurally similar to jervine [98] – was first found in Fritillaria roylei [99], but its structure was not established. This alkaloid was later isolated from the plant Petilium eduardi [40]. The chemical transformation and NMR and mass spectra of peimisine permit the conclusion that it contains the jervanine heterocyclic skeleton [42]. The presence in the NMR spectra of peimisine and of O,N-diacetylpeimisine of singlets at 1.56 and 1.65 ppm, respectively, and also the presence in the mass spectrum of peaks of ions with m/e 110, 124, and 125 show that the double bond in peimisine is present C_{12}-C_{13}. The difference in the CSs of the 19-CH_3 protons between peimisine, on the one hand, and O,N-diacetylpeimisine and dihydropeimisine, on the other hand, shows that the hydroxy group in peimisine is located at C_3 and has the β-orientation, and the carbonyl group is present at C_6. On the basis of a comparative study of the CSs of the protons of the secondary and tertiary methyl groups in the NMR spectra of peimisine and its transformation products with those of jervine, structure and configuration (65) have been suggested for peimisine [42].

The acetylation of edpetine forms O,N-diacetyledpetine. A comparison of the CSs of the protons of the methyl, methylene, and methine groups in the NMR spectra of O,N-diacetyledpetinine and of O,N-diacetylpeimisine shows that the hydroxy groups in edpetine are present at C_3-β and C_{14}-α, and the carbonyl group at C_6; there is no 18-CH_3 group or double bond between C_{12} and C_{13}, but in place of the 18-CH_3 methyl group there is

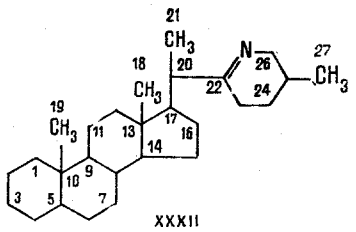
a terminal methylene group at C_{13}. Structure and configuration (66) have been suggested for edpetine [46].

Korsevine (67) is also assigned to the jervine group, but in contrast to peimisine and jervine, korsevine has no ether bridge at C_{17}-C_{23} and contains a N-CH_3 group. The presence in the mass spectrum of korsevine of peaks of ions with m/e 112, 287, 314, and 316 and the features of its NMR spectra show that the double bond is between C_{12} and C_{13} and there is a β-oriented hydroxy group at C_3 and a carbonyl group at C_6 [56].

II. TYPICAL STEROID ALKALOIDS

1. Verazine Group

The alkaloids of the verazine group are found in the plants of the genera Veratrum and Solanum and in the plants Petilium raddeana and Korolkowia sewerzowii. They are encountered in nature in the form of free amino alcohols, ester glycoalkaloids, and glycoalkaloids. Eleven alkaloids from the genus Veratrum, one from Petilium raddeana, and two from Korolkowia sewerzowii belong to the verazine group. These alkaloids are based on the 22,26-iminocholestane heterocyclic skeleton (XXXII).



XXXII

The oxygen atoms in the alkaloids are present in hydroxy or carbonyl groups or form oxygen bridges between the C_{23} and C_{26} atoms, apart from those in ester groupings and sugar residues [59, 72, 76, 100, 101]. The structures and configurations of the alkaloids of this group have been shown mainly by physical methods of investigation [102]. The NMR spectra of the alkaloids of the verazine group show the signals from the protons of two tertiary methyl groups at 0.63-0.75 ppm (18-CH_3) and 0.68-1.0 ppm (19-CH_3), and two secondary methyl groups at 0.83-0.98 ppm (21-CH_3) and 1.0-1.12 ppm (27-CH_3) [72, 76. 102, 103]. In the NMR spectrum of the O,N-diacetyl derivatives, as well as the signals of acetoxy groups an additional signal appears at 5.05-5.20 ppm from an olefinic proton. This is explained by the fact that the O,N-diacetyl derivatives are formed as the result of the migration of the C = N double bond to the $\Delta^{22(23)}$ position and the migration of hydrogen from C_{23} to the nitrogen atom.

The UV spectrum of veralosidine (XXXIII), λ_{max} 242 nm (log ε 2.45), is similar to that of verazine. In the mass spectrum of veralosidine there are the characteristic peaks of ions with m/e 98, 111, 125 (100%), 138, 162, and 413 (M^+), as in the mass spectra of verazine and petiline [72, 76].

The production of an α,β-unsaturated ketone in the Oppenauer oxidation of veralosidine, the formation of a sparingly soluble digitonide, and absorption in the IR spectrum at about 1060 cm^{-1} show that there is a β-oriented OH group at C_3 and a double bond at C_5-C_6 [72, 77, 103].

In veralosinine (XXXIV), veralodisine (XXXV), and veralosidinine as well, in each case an OH group occupies the C_3 position and there is a C_5-C_6 double bond [19, 24].

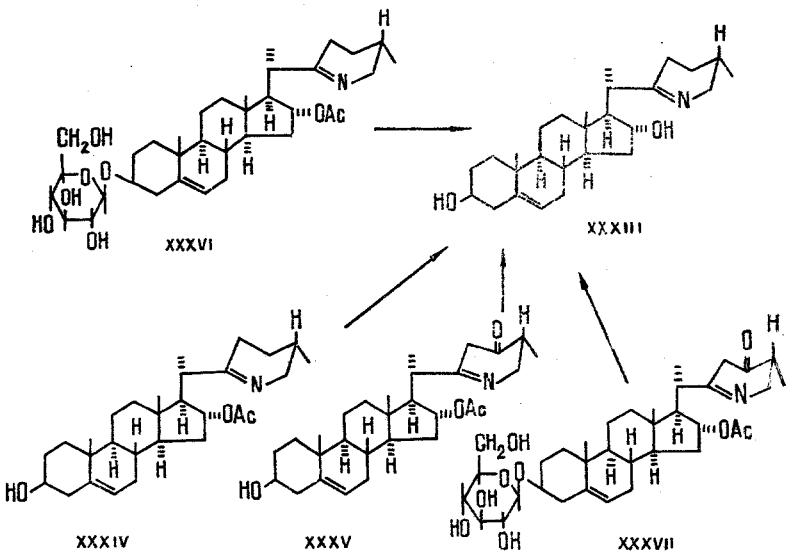
In the NMR spectra of di- and triacetylveralosidines and of dihydroveralosidine the signals of the protons from the C-18 methyl group have an upfield displacement by 0.14-0.20 ppm and the signal of the C-16 proton geminal to the hydroxy and acetoxy groups one of 0.17-0.35 ppm as compared with the corresponding signals in the spectra of di- and triacetylpseudosolasodines and dihydrosolasodenol. From this it may be concluded that the second hydroxy group is present at C_{16} and has the α-orientation.

It has been shown by a comparative study of the NMR spectra of di- and triacetylveralosidines and dihydroveralosidine with the NMR spectra of the model compounds di- and triacetylpseudosolasodines and dihydrosolasodenol that the 21-CH_3 methyl group and the hydrogen at C_{17} have the α-orientation, just as in solasodine and its transformation products [19, 93].

The circular dichroism (CD) spectrum of veralosidine shows a negative Cotton effect (CE) at 235 nm due to a transition in the azomethine chromophore. The negative sign of this CE shows that veralosidine belongs to the 25S series and the azomethine ring has the same configuration as in verazine [72, 104]. Thus, for veralosidine a structure and configuration have been established which differ from those of verazine by the presence of a C_{16}-α-oriented hydroxy group [19, 104]. It follows from the NMR spectra that in typical steroid alkaloids a pro-

ton geminal to an acetoxy group in the five-membered ring D resonates in the 4.69-5.13 ppm region, while in a six-membered ring an analogous proton resonates at 4.46-4.62 ppm, and a 16β-oriented hydroxy or acetyl group cause a paramagnetic shift of the signal of the 18-CH_3 group by 0.14-0.20 ppm as compared with α-oriented C_{16}-hydroxy and acetoxy groups [19, 23]. Veralosinine is an ester alkaloid, and veralosine (XXXVI) is an ester glycoalkaloid derived from veralosidine [18, 19]. Veralosidinine [23] differs from veralosinine by the presence of a 15β-hydroxy group, and veralodisine differs by the presence of a carbonyl group. The reduction of veralodisine with lithium tetrahydroaluminate gives tetrahydroveralodisinol. In the mass spectrum of tetrahydroveralodisinol the maximum peak of an ion with m/e 114 shows the presence of a carbonyl group in its ring F at C_{24} [59, 80, 103].

In veralodinine (XXXVII) a carbonyl group is again present at C_{24}, and there is a D-glucose residue at C_3 [25]. The transition from veralosinine, veralosine, veralodisine, and veralodinine to veralosidine has been effected.



From their chemical properties and spectral characteristics, petiline, korsevinine, and korsiline also have the 22,26-iminocholestane skeleton. The displacement of the signals from the protons of the 19-CH_3 group in the NMR spectra of petiline, korsevinine, and korsiline and their hydrogenated, acetyl, and deoxo derivatives shows that in their molecules there is a β-oriented OH group at C_3 and a carbonyl group at C_6 [59, 67, 76].

The presence of an O-bond in ring F at C_{23}-C_{26} in korsevinine is shown by the appearance of a strong peak of an ion with m/e 114 in the mass spectrum of hexahydrokorsevenine [59, 103].

Korsiline is a diastereoisomer of petiline. Korsiline apparently differs from petiline at the C_{20} or C_{25} asymmetric center [67, 76].

2. New Types of Steroid Alkaloids

Veralkamine, edpetilidinine, and veracintine belong to new types of steroid alkaloids. In alkaloids of the veralkamine type, the 18-CH_3 group is present at C_{17} and not C_{13}. In the edpetilidinine type the nitrogen-containing ring F is seven-membered, and in veracintine it is five-membered [40, 71, 73, 105].

In the NMR spectra of the alkaloids of the veralkamine type, the signals of the protons of two tertiary methyl groups are observed at 0.92-0.96 ppm (19-CH_3) and 0.96-1.02 ppm (18-CH_3) and those of two secondary methyl groups at 0.81-0.84 ppm (21-CH_3) and 0.96 ppm (27-CH_3) [106-108]. Olefinic protons at C_6 and C_{12} give signals in the 5.25-5.32 ppm region. In the tetrahydro derivatives of the alkaloids, the signals from the protons of the C-19 and C-18 methyl groups are shifted upfield by 0.19 and 0.07 ppm, respectively. The presence of a Δ^5 bond in an alkaloid is established from the chemical shifts of the protons of the 19-methyl group and the magnitude of the difference between the molecular rotations of the alkaloid and its dihydro derivative [93, 109].

In the mass spectrum of an alkaloid of the veralkamine series, a fragment with m/e 98 shows the presence of a C-methylpiperidine nucleus in its molecule, and a strong peak with m/e 114 is characteristic for the spirosolane alkaloids [78].

Veralomine is a glycoalkaloid. On hydrolysis it gives the aglycone veralomidine, the anhydro compound veralomidene, and D-glucose [28].

The structure of veralomidine has been established by comparing its chemical properties and spectral characteristics with those of veralinine [107]. Veralomine has the structure of 3β-O-D-glucopyranosylveralomidine [28]. For edpetilinine the structure of 3β-O-xylopyranosyledpetilidinine and for sevcorine that of 3β-O-D-glucopyranosylsevcoridinine have been established [45, 57, 61]. The absence of a signal from the protons of the 27-CH_3 groups in the NMR spectra of edpetilidinine and of sevcoridinine and the characteristics of the mass spectra show that their molecules contain an N-methylhexamethylenamine ring [61, 105].

In the NMR spectra of edpetilidinine and of diacetyledpetilidinine the signals from two olefinic protons in the form of a triplet, and also fragments with m/e 125 and 138 in their mass spectra, show that the double bond is located at C_{15}-C_{16}. According to the NMR spectra of edpetilidinine and diacetyledpetilidinine, β-oriented hydroxy groups are present at C_3 and C_6 in each case. In sevcoridinine the double bond and β-oriented hydroxy groups are present in the same positions as in edpetilidinine. Sevcoridinine is a diastereoisomer of edpetilidinine at the C_{20} and C_{22} asymmetric center, the configurations of these centers not having been established for either alkaloid [61, 105].

Thus, plants of the genera Veratrum, Petilium, and Korolkowia contain C-nor-D-homosteroids and typical steroid alkaloids, these being derivatives of 1,2-benzofluorene and of 3-methyl-1,2-cyclopentenophenanthrene, respectively. The representatives of these steroid alkaloids have been separated into groups and have their own characteristic reactions and spectra.

The study of the alkaloids of V. lobelianum, P. eduardi, and K. sewerzowii has shown that these plants produce a large number of alkaloids of complex structure, many of which also contain readily hydrolyzable groupings such as α-ketol, glycoside, ester, etc., groupings. Consequently, the isolation and separation of these alkaloids are associated with certain difficulties and require special approaches.

Among the plants studied, particular interest is presented by V. lobelianum, the alkaloids of which possess peculiar structural modifications of this class of compounds (germine, jervine, verazine, veralkamine, veracintine, solanidine). N-Oxides, ester glycoalkaloids, and alkaloids with 16-acetoxy groups have been found among steroid alkaloids for the first time.

The sugar moieties of the steroid glycoalkaloids are present in the pyranose form and are attached through the hydroxy groups at C_3. In a typical steroid alkaloid a gem-acetoxy proton in a five-membered ring resonates in a weaker field than in the six-membered ring, and 16β-hydroxy and -acetoxy groups cause a paramagnetic shift of the signal of the 18-CH_3 methyl group as compared with α-oriented C_{16}-hydroxy and -acetoxy groups.

The isolation from V. lobelianum of bases belonging to different groups of typical steroid alkaloids and C-nor-D-homosteroid alkaloids has permitted the conclusion that in this plant a biogenetic interrelationship possibly exists between the typical steroid alkaloids and the C-nor-D-homosteroid alkaloids.

The facts obtained in the investigation of three species of plants once again confirmed the rule deduced previously by S. Yu. Yunusov that each plant organ may contain qualitatively and quantitatively different alkaloids according to the growth site and vegetation period [147]. The alkaloids and their derivatives found in plants of the genera Veratrum, Petilium, and Korolkowia have exhibited physiological activity as hypotensive, anti-inflammatory, bronchodilator, and spasmolytic agents.

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